



Chalmers, J. R., Haines, R. H., Bradshaw, L. E., Montgomery, A. A., Thomas, K. S., Brown, S. J., Ridd, M. J., Lawton, S., Simpson, E. L., Cork, M. J., Sach, T. H., Flohr, C., Mitchell, E. J., Swinden, R., Tarr, S., Davies-Jones, S., Jay, N., Kelleher, M. M., Perkin, M. R., ... BEEP study team (2020). Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. *Lancet*, 395(10228), 962-972. [https://doi.org/10.1016/S0140-6736\(19\)32984-8](https://doi.org/10.1016/S0140-6736(19)32984-8)

Publisher's PDF, also known as Version of record

License (if available):
CC BY

Link to published version (if available):
[10.1016/S0140-6736\(19\)32984-8](https://doi.org/10.1016/S0140-6736(19)32984-8)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the final published version of the article (version of record). It first appeared online via Elsevier at [https://doi.org/10.1016/S0140-6736\(19\)32984-8](https://doi.org/10.1016/S0140-6736(19)32984-8) . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>



Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial



Joanne R Chalmers, Rachel H Haines, Lucy E Bradshaw, Alan A Montgomery, Kim S Thomas, Sara J Brown, Matthew J Ridd, Sandra Lawton, Eric L Simpson, Michael J Cork, Tracey H Sach, Carsten Flohr, Eleanor J Mitchell, Richard Swinden, Stella Tarr, Susan Davies-Jones, Nicola Jay, Maeve M Kelleher, Michael R Perkin, Robert J Boyle, Hywel C Williams on behalf of the BEEP study team

Summary

Background Skin barrier dysfunction precedes eczema development. We tested whether daily use of emollient in the first year could prevent eczema in high-risk children.

Methods We did a multicentre, pragmatic, parallel-group, randomised controlled trial in 12 hospitals and four primary care sites across the UK. Families were approached via antenatal or postnatal services for recruitment of term infants (at least 37 weeks' gestation) at high risk of developing eczema (ie, at least one first-degree relative with parent-reported eczema, allergic rhinitis, or asthma, diagnosed by a doctor). Term newborns with a family history of atopic disease were randomly assigned (1:1) to application of emollient daily (either Diprobase cream or DoubleBase gel) for the first year plus standard skin-care advice (emollient group) or standard skin-care advice only (control group). The randomisation schedule was created using computer-generated code (stratified by recruiting centre and number of first-degree relatives with atopic disease) and participants were assigned to groups using an internet-based randomisation system. The primary outcome was eczema at age 2 years (defined by UK working party criteria) with analysis as randomised regardless of adherence to allocation for participants with outcome data collected, and adjusting for stratification variables. This trial is registered with ISRCTN, ISRCTN21528841. Data collection for long-term follow-up is ongoing, but the trial is closed to recruitment.

Findings 1394 newborns were randomly assigned to study groups between Nov 19, 2014, and Nov 18, 2016; 693 were assigned to the emollient group and 701 to the control group. Adherence in the emollient group was 88% (466 of 532) at 3 months, 82% (427 of 519) at 6 months, and 74% (375 of 506) at 12 months in those with complete questionnaire data. At age 2 years, eczema was present in 139 (23%) of 598 infants with outcome data collected in the emollient group and 150 (25%) of 612 infants in the control group (adjusted relative risk 0.95 [95% CI 0.78 to 1.16], $p=0.61$; adjusted risk difference -1.2% [-5.9 to 3.6]). Other eczema definitions supported the results of the primary analysis. Mean number of skin infections per child in year 1 was 0.23 (SD 0.68) in the emollient group versus 0.15 (0.46) in the control group; adjusted incidence rate ratio 1.55 (95% CI 1.15 to 2.09).

Interpretation We found no evidence that daily emollient during the first year of life prevents eczema in high-risk children and some evidence to suggest an increased risk of skin infections. Our study shows that families with eczema, asthma, or allergic rhinitis should not use daily emollients to try and prevent eczema in their newborn.

Funding National Institute for Health Research Health Technology Assessment.

Copyright © 2020 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Eczema (additionally termed atopic dermatitis or atopic eczema) affects about one in five children,¹ is increasing in prevalence, and confers a high disease burden for individuals and their carers.² Eczema usually starts in infancy, and persistence into adulthood is common.³ Children with eczema are more likely to develop other atopic conditions including food allergies, asthma, and allergic rhinitis.⁴ Because eczema usually precedes the development of food allergy, and early onset eczema is strongly associated with food allergy, prevention of eczema could prevent the development of food allergy.^{5,6}

Eczema is associated with loss-of-function mutations in *FLG*, the gene encoding filaggrin—a multi-functional

protein that contributes to skin barrier integrity.⁷ This suggests that an impaired skin barrier could be a key defect in eczema development.^{7,8} Sensitisation to food allergens can occur via a defective skin barrier.^{9–14} Several observations support the rationale for emollients as a primary prevention intervention for eczema. Skin barrier dysfunction is apparent soon after birth and precedes eczema development, providing an opportunity for strategies to improve skin hydration and barrier function.^{15,16} Emollients render the skin less susceptible to irritants such as soaps and detergents that could initiate eczema, can reduce percutaneous sensitisation by food antigens,^{8,15} and can prevent flares of eczema (secondary prevention).¹⁷ Two small randomised pilot

Lancet 2020; 395: 962–72

Published Online

February 19, 2020

[https://doi.org/10.1016/S0140-6736\(19\)32984-8](https://doi.org/10.1016/S0140-6736(19)32984-8)

See [Comment](#) page 923

Centre of Evidence Based

Dermatology (J R Chalmers PhD,

Prof K S Thomas PhD,

S Davies-Jones, R J Boyle PhD,

Prof H C Williams DSc) and

Nottingham Clinical Trials Unit

(R H Haines MA,

L E Bradshaw MSc,

Prof A A Montgomery PhD,

E J Mitchell BA, R Swinden,

S Tarr BSc), University of

Nottingham, Nottingham, UK;

Skin Research Group, School of

Medicine, University of

Dundee, Dundee, UK

(Prof S J Brown MD);

Department of Dermatology,

Ninewells Hospital and Medical

School, Dundee, UK

(Prof S J Brown); Population

Health Sciences, University of

Bristol, Bristol, UK

(M J Ridd PhD); Rotherham NHS

Foundation Trust, UK

(S Lawton MSc); Department of

Dermatology, Oregon Health

and Science University,

Portland, OR, USA

(Prof E L Simpson MD); Sheffield

Dermatology Research,

Department of Infection and

Immunity, University of

Sheffield, Sheffield, UK

(Prof M J Cork PhD); Health

Economics Group, Norwich

Medical School, University of

East Anglia, Norwich Research

Park, Norwich, UK

(Prof T H Sach PhD); Unit for

Population-Based

Dermatology Research,

St John's Institute of

Dermatology, Guy's &

St Thomas' NHS Foundation

Trust and King's College

London, London, UK

(Prof C Flohr PhD); Sheffield

Children's Hospital, Sheffield,

UK (N Jay MSc); National Heart

and Lung Institute, Imperial

College London, London, UK

(M M Kelleher MD, R J Boyle);

and St George's, University of

Research in context

Evidence before this study

Genetic discoveries suggest that enhancing the skin barrier from birth might prevent eczema. In 2014, our pilot trial of 124 infants born to high-risk families suggested that daily emollients used for 6 months after birth could reduce development of eczema by around 50%. A similar study of 118 neonates in Japan found similar results with a 32% reduction in eczema at 32 weeks. We therefore designed the barrier enhancement for eczema prevention (BEEP) study to determine the effectiveness of advice to use emollients daily for the first year of life to prevent eczema in infants born to high-risk families. We searched the Centre of Evidence-Based Dermatology maps of systemic reviews of eczema prevention and Cochrane Central Register of Controlled Trials, MEDLINE, and online trial registries from Jan 1, 2000, until Aug 25, 2019, with no language restrictions, using synonyms for trials: "randomized controlled trial", "controlled clinical trial", "randomized", "placebo", "randomly", "trial"; and for eczema: "dermatitis" or "eczema" or "neurodermatitis" or "besnier" and "prevention".

We found 102 systematic reviews on eczema prevention but none dealing with barrier enhancement. Two randomised controlled trials of emollients for prevention of eczema have been published since our search: one from Japan including 459 infants (which tested Locobase REPAIR cream, Daiichi Sankyo, Japan) and the second from the USA including 100 infants (which tested Cetaphil Restoraderm, Galderma Laboratories, TX, USA). These two studies used ceramide-containing emollients, neither of which showed any significant preventive effect against development of eczema.

Several additional ongoing trials investigating skin barrier interventions for eczema prevention have been identified, one of which (PreventADALL) is reported in this issue.

Added value of this study

The BEEP study of 1394 infants, the first large randomised controlled trial to specifically investigate whether emollients could prevent eczema, found no evidence to support the hypothesis that advice to use daily emollients can prevent eczema (primary outcome), food allergy, sensitisation, allergic rhinitis, or wheezing (secondary outcomes), and some evidence to suggest an increase in skin infections in those using emollients. Given the demanding nature of asking parents to apply emollients to the whole body for 12 months, we were pleased with reported adherence proportions of 88%, 82%, and 74% at 3 months, 6 months, and 12 months respectively.

Implications of all the available evidence

Since the publication of the two small efficacy studies, health-care professionals have started to recommend emollient for the primary prevention of eczema in high-risk families. This large, pragmatic study suggests that emollients used in this way do not prevent eczema and might be associated with harm, and that such practices should be stopped unless new evidence suggests otherwise. Knowledge of the neonatal skin barrier and optimal emollient formulation has progressed since the BEEP study was initiated, so new products might potentially exert a protective effect, which could be enhanced if accompanied by additional measures such as soft water and avoidance of soap.

London, London, UK
(M R Perkin PhD)

Correspondence to:
Prof Hywel C Williams, Centre of
Evidence Based Dermatology,
University of Nottingham,
Nottingham, NG7 2NR, UK
hywel.williams@nottingham.ac.uk

trials provided evidence that eczema prevention through emollients might be possible.^{13,14} One study¹³ of 124 infants at high risk of eczema born in the UK and the USA showed that 22% of infants advised to use daily emollients developed eczema by age 6 months compared with 43% in controls (relative risk [RR] 0.50, 95% CI 0.28–0.90). The second study¹⁴ included 118 high-risk infants in Japan and showed that 32% of infants in the intervention group had eczema after 32 weeks versus 47% in the control group (hazard ratio 0.48, 95% CI 0.27–0.86). These strong efficacy signals from two small studies underpinned the decision of our funders to support a large-scale pragmatic trial to assess whether this intervention was effective when tested in normal practice.

Simple emollient formulations are inexpensive, widely available, and used extensively for treating eczema, and if effective in preventing eczema, could represent a breakthrough in reducing eczema incidence globally. We undertook this large, pragmatic trial to test the hypothesis that emollient use in the first year of life in high-risk infants (ie, with a family history of atopic disease) can prevent eczema and other atopic diseases including food allergy.

Methods

Study design and participants

This was a multicentre, two-arm, parallel-group, randomised controlled trial that was done at 12 hospitals and four primary care sites across the UK (appendix p 3). Families were approached largely via antenatal or postnatal services, by invitation letters from their general practitioners (GP), and through posters describing the study in hospitals and the community. Term infants (at least 37 weeks' gestation) at high risk of developing eczema (ie, at least one first-degree relative with parent-reported eczema, allergic rhinitis, or asthma diagnosed by a doctor) were included. Other inclusion criteria were mother aged 16 years or older, and the consenting adult had to have the ability to understand English. Exclusion criteria were as follows: preterm birth (birth before 37 weeks' gestation); a sibling (including twin) randomly assigned in the trial; a severe widespread skin condition that would make detection or assessment of eczema difficult; a serious health issue that would make it difficult for the family to take part in the trial; and a condition that would make the use of emollient inadvisable. Screening was usually done during the third trimester or shortly after delivery, and most

See Online for appendix

families chose for this screening to take place in the family home.

Informed consent was obtained from mothers during pregnancy, or from the mother, father, or guardian after delivery. The trial was overseen by an independent Trial Steering Committee (appendix p3) and approved by the West Midlands Ethics Committee, UK (14/WM/0162). The study was sponsored by the University of Nottingham, coordinated by the Nottingham Clinical Trials Unit (CTU), and funded by the UK National Institute for Health Research (NIHR) Health Technology Assessment Programme. Supplementary funding was obtained for inclusion of food allergy outcomes and skin prick tests subsequent to study initiation, which was provided by Goldman Sachs Gives and Sheffield Children's Hospital Charity. The full protocol and changes made after the trial started are available online on the trial website and in the appendix (p 10). A protocol summary was published previously.¹⁸

Randomisation and masking

Infants were randomly assigned (1:1) to receive either emollient and best practice skin-care advice (emollient group) or best practice skin-care advice only (control group). Infants were randomly assigned to a group within a maximum of 21 days after delivery, and randomisation was stratified by recruiting centre and number of first-degree relatives with atopic disease (1, 2, or >2). The randomisation schedule was created by the CTU using computer-generated pseudo-random code with permuted blocks of randomly varying size. The sequence was known only to the programmer until database lock. Research nurses randomly assigned participants to groups using a secure, internet-based randomisation system developed and maintained by the CTU. Parents were informed of their child's allocation by staff at the CTU. Research nurses doing skin examinations, skin prick testing, food challenges, or making food allergy decisions, and the statistician, were masked to treatment allocation during the study. Interim follow-up at 2 weeks and at 3, 6, 12, and 18 months was done by CTU staff to maintain research nurse masking. Participating families were not masked.

Procedures

Families in the intervention group could choose between Doublebase Gel (Dermal Laboratories, Herts, UK) or Diprobase Cream (Bayer, Berks, UK). They were sent an initial package containing both emollients and parents specified on their resupply instructions which of the two emollients they wished to receive. Parents were advised to apply emollient to their child at least once daily to the whole body (excluding the scalp) until the child reached 1 year of age. They were also advised to apply emollient after every bath, even if they had already applied the emollient that day. Daily application was advised to encourage regular use of emollient several times a week, but because the study was designed to

reflect how the intervention might be delivered in normal practice, no prompts or reminders were sent to parents. Parents were advised to stop applying emollients when their child reached 1 year of age, and no further emollients were supplied after this point.

Both groups received advice on general skin care in booklet and video format at the time of randomisation (appendix pp 11–21). The skin care guidance provided advice to use mild cleansers and shampoos specifically formulated for infants, and to avoid soap, bubble bath, and baby wipes.¹⁹ The guidance given to those in the emollient group also showed parents how to apply emollients correctly by dotting over the skin and using gentle downward strokes rather than rubbing in and contained warnings about the skin being slippery after application and the need to clean up spillages from the floor to avoid slipping. Parents were advised to seek medical advice as they would normally do if their child developed skin problems.

Follow-up was at 2 weeks (by telephone) and at 3, 6, 12, and 18 months (online or postal questionnaire). At the 2-year follow-up visit, the masked research nurse did the skin examination, saliva sample collection, skin prick testing, and provided the questionnaires, usually in the family home. In cases for whom a visit was not possible, data were collected by telephone, email, SMS, postal questionnaire, or from the GP. Methods for saliva collection, DNA extraction, and skin prick testing were published previously.^{18,20} DNA samples were genotyped for the four most common *FLG* null mutations in the white European population (2282del4, R501X, S3247X, and R2447X).²¹ Participants who had a positive skin-prick test or a history suggestive of food allergy and in whom further investigation was required for a diagnosis of food allergy to be made were invited for a supervised oral food challenge. Food challenges were done at two hospitals by experienced allergy nurses masked to treatment allocation, following standard procedures.

Outcomes

The primary outcome was diagnosis of eczema over the past year (defined by the UK working party refinement of the Hanifin and Rajka diagnostic criteria for eczema) assessed by research nurses masked to treatment allocation at age 2 years.²² This timepoint of 1 year after the intervention ended was chosen to ensure that the emollient had a genuine and lasting protective effect on eczema incidence as opposed to masking the emergence of mild eczema that might have occurred because of emollient use during year 1.^{23,24}

Secondary eczema outcomes were other eczema definitions—ie, presence of eczema between birth and 2 years of age (assessed by any parental report of a clinical diagnosis of eczema [up to 2 years] and parent completion of UK working party criteria at 1 and 2 years), presence of visible eczema at 2 years recorded by a nurse who was masked to treatment allocation; time to onset of eczema

For more on the BEEP study see
<https://www.nottingham.ac.uk/research/groups/cebd/projects/1eczema/beep-maintrial.aspx>

(based on first parent report of clinician diagnosis and time of first topical corticosteroid or immunosuppressant prescription); clinician-reported and patient-reported severity of eczema (Eczema Area and Severity Index [EASI] at 2 years and Patient-Oriented Eczema Measure [POEM] at 1 and 2 years). Other secondary outcomes were presence of other allergic diseases (ie, parent-reported wheezing and allergic rhinitis [between 1 and 2 years]; allergic sensitisation [masked skin prick tests] to milk, egg, peanut, cat dander, grass pollen, or dust mite at 2 years; parent-reported food allergy and parental report of clinical diagnosis of food allergy at 1 and 2 years; and allergy to milk, egg, or peanut at 2 years confirmed either by oral food challenge or for cases in which no oral food challenge

was done, an expert allergy panel masked to treatment allocation). The expert panel decisions were made using a validated algorithm adapted from the EAT trial, which incorporates all available data including skin-prick test results, previous reaction history, frequency of food ingestion, and allergy tests done outside the trial.²⁵ Safety outcomes were parent-reported skin infections (parents were asked what the doctor called the infection) and emollient-related infant slippages during the intervention period (year 1).

Analysis of health economic outcomes is underway and will be published separately. This will include analysis of health-care resource use at 3, 6, 12, 18, and 24 months, and cost-effectiveness and cost-utility at 24 months.

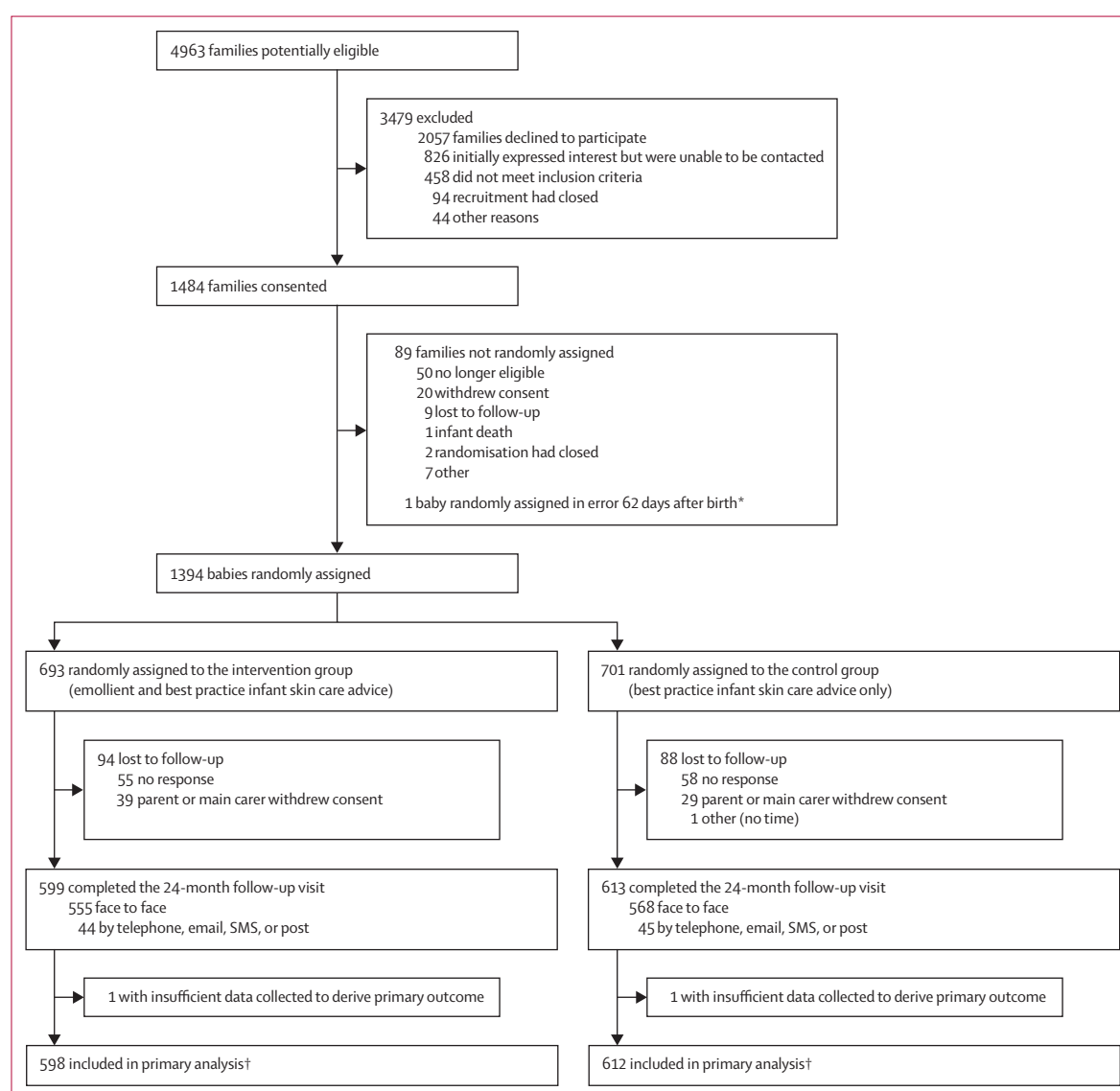


Figure 1: Trial profile

*One family was randomly assigned in error at 62 days after birth and so was not included further. The family was not informed of the randomisation, not sent any intervention, and was not contacted for any follow-up. †A sensitivity analysis including all participants was also done using multiple imputation for missing data.

Quality of life was measured by Child Health Utility (CHU-9D) at 2 years to estimate quality-adjusted life-years (QALYs) in infants, and by EQ-5D-5L for parents at baseline and 2 years to estimate parental QALYs.

Adherence was captured at each questionnaire timepoint during year 1 (3, 6, and 12 months) by asking parents about emollient use since the last questionnaire (appendix p 4), and was defined in the protocol as satisfactory in the intervention group if emollients were applied at least 3–4 times per week to most of the child's body (defined as at least two of face and neck, arms and legs, or trunk). A similar definition was used for contamination in the control group.

For the statistical analysis plan see <https://www.nottingham.ac.uk/research/groups/cebd/documents/researchdocs/0935-beep-sap-final-v1.0-20181205-signed.pdf>

	Emollient group (n=693)	Control group (n=701)
Age of mother at randomisation (mean [SD])	31·7 (5·3)	31·5 (5·2)
Parental-reported number of first-degree relatives with atopic disease		
1	254 (37%)	253 (36%)
2	300 (43%)	296 (42%)
3 or more	139 (20%)	152 (22%)
At least one first-degree relative with history of eczema (parent report of doctor diagnosis)	563 (81%)	580 (83%)
Mother has eczema or had a history of eczema (parent report of doctor diagnosis)	348 (50%)	372 (53%)
Singleton pregnancy*	690 (100%)	696 (99%)
Gestation at birth in weeks (median [IQR])	40 [39·1–40·9]	40 [39·0–40·9]
Ethnicity of mother		
White	589 (85%)	601 (86%)
Asian	45 (6%)	40 (6%)
Black	31 (4%)	22 (3%)
Other	28 (4%)	38 (5%)
Decile of English index of multiple deprivation 2015 (median [IQR])	6 (3–9)	6 (3–8)
No other children living in household at screening	275 (40%)	293 (42%)
Sex		
Male infant	374 (54%)	359 (51%)
Female infant	319 (46%)	342 (49%)
Vaginal delivery	482 (70%)	472 (67%)
Furry pets living in house at time of birth	295 (43%)	302 (43%)
Maternal antibiotics during pregnancy	210 (30%)	201 (29%)
Maternal probiotics during pregnancy (collected at 6 months)	33/511 (6%)	32/505 (6%)
FLG genotyping†		
Number of infants	402	414
+/+ (no mutations)	339/402 (84%)	352/414 (85%)
+/- (one FLG null mutation)	62/402 (15%)	60/414 (14%)
-/- (two FLG null mutations)	1/402 (<1%)	2/414 (<1%)

Data presented are n (%) or n/N (%) unless otherwise specified. FLG= gene encoding filaggrin. *Three cases in the emollient group and five cases in the control group were twin and higher-order pregnancies. †FLG genotype obtained from saliva samples at 2-year visit for infants whose parents consented to this part of the study. Samples were tested for the four most prevalent FLG loss-of-function mutations in the white European population. Of the 816 children included in the analysis, 810 (400 in the emollient group and 410 in the control group) had both parents of white ethnicity and six (two in the emollient group and four in the control group) had parents not of white ethnicity, but were included in the analysis because an FLG null mutation was detected.

Table 1: Baseline characteristics

Analysis and publication of data for the 2-year primary outcome timepoint were preplanned. Data collection for long-term outcomes at 3, 4, and 5 years is ongoing, but the trial is closed to recruitment of new participants.

Statistical analysis

The trial was designed to detect a relative reduction of 30% in eczema at the 5% significance level (two-sided) with 90% power based on an expected rate of eczema of 30% in the control group and 20% attrition, resulting in a sample size of 1282.¹⁸ Quicker than expected recruitment prompted a review by the Trial Steering Committee (August, 2016), who permitted all pregnant mothers who had already given consent by that point to be randomly assigned to a study group upon the birth of the baby, allowing for a maximum recruitment total of 1400.

We analysed participants as randomised regardless of adherence with allocation and using observed data. The adjusted RR and difference in risk for the primary outcome were estimated using Generalised Estimating Equations with the Binomial family and log/identity link respectively, with an exchangeable correlation matrix to account for randomisation being stratified by centre and number of immediate family members with atopic disease (1, 2, or >2) included as a covariate. Sensitivity analyses were done using multiple imputation for missing data to include all participants in the analysis, split according to method of data collection (in person or by telephone, email, SMS, or post) and actual emollient use (complier average causal effect [CACE] accounting for emollient use in both groups). Analyses of secondary and safety outcomes used appropriate regression models and adjusted for stratification variables. Subgroup analyses for the primary outcome (diagnosis of eczema) and the secondary outcome of confirmed food allergy were done by including an interaction term in the analysis model for FLG genotype, number of first-degree relatives with atopic disease, and number of first-degree relatives with eczema. Additional subgroup analyses for the primary outcome for season of birth, water hardness in the home, and parent-reported probiotic supplements during pregnancy were in the statistical analysis plan (SAP) but not the protocol. Further details are presented in the appendix and SAP, finalised before the database lock. Analyses were done with Stata version 15.1. The trial was registered at the ISRCTN registry before initiation of recruitment, ISRCTN21528841.

Role of the funding source

The main funder (NIHR Health Technology Assessment) was involved in refining the trial design through the funding peer review process, but had no role in data collection, data analysis, data interpretation, or writing of the report. The funders of the food allergy outcomes and skin prick tests (Goldman Sachs Gives and Sheffield Children's Hospital Research Fund) had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. HCW, AAM,

	Emollient group	Control group	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Diagnosis of eczema at age 2 years according to UK working party diagnostic criteria*	139/598 (23%)	150/612 (25%)	0.95 (0.78 to 1.16)	-1.2% (-5.9 to 3.6)
Secondary eczema outcomes				
At age 2 years				
Masked assessment of visible eczema at age 2 years	151/555 (27%)	149/568 (26%)	1.05 (0.86 to 1.27)	1.1% (-4.0 to 6.3)
Parent report of a clinical diagnosis of eczema between birth and age 2 years	266/610 (44%)	282/616 (46%)	0.96 (0.85 to 1.08)	-2.0% (-7.5 to 3.6)
Eczema according to UK working party diagnostic criteria (parent completion)	187/599 (31%)	195/612 (32%)	0.98 (0.83 to 1.16)	-0.5% (-5.7 to 4.8)
Moderate, severe, or very severe eczema according to EASI	9/553 (2%)	10/567 (2%)	0.93 (0.38 to 2.27)	0.0% (-1.5 to 1.4)
Moderate, severe, or very severe according to POEM	58/576 (10%)	51/595 (9%)	1.18 (0.82 to 1.68)	1.7% (-1.6 to 5.0)
At age 1 year				
Eczema according to UK working party diagnostic criteria (parent completion)	103/516 (20%)	107/527 (20%)	0.98 (0.77 to 1.25)	-0.3% (-5.1 to 4.6)
Moderate, severe, or very severe according to POEM	52/512 (10%)	49/522 (9%)	1.09 (0.75 to 1.57)	1.0% (-2.5 to 4.6)

Data are n/N (%) unless otherwise specified. The adjusted relative risk and difference in risk are estimated using generalised estimating equations with the binomial family and log/identity link respectively, with an exchangeable correlation matrix to account for randomisation being stratified by centre and number of immediate family members with atopic disease (1, 2, or more than 2) included as a covariate. EASI=Eczema Area and Severity Index. POEM=Patient-Oriented Eczema Measure. *p=0.61.

Table 2: Primary and secondary eczema outcomes

and LEB had full access to all the data in the study, and HCW had final responsibility for the decision to submit for publication.

Results

Between Nov 19, 2014, and Nov 18, 2016, 4963 families were assessed for eligibility at 12 hospitals and four general practice sites in the UK. 1394 babies were randomly assigned (1:1) to study groups (693 to the emollient group and 701 to the control group; figure 1). Baseline characteristics were balanced across groups (table 1). Accidental unmasking of outcome assessors to treatment allocation occurred for 3% of families at the 2-year visits (41 of 1190 participants who completed follow-up in person, or via telephone, text, or email; 30 in the emollient group and 11 in the control group). 509 families in the emollient group responded to a telephone call to check they had received the skin-care pack and emollients, and to collect data on the date they started applying the emollient to the infant. The median age of those in the emollient group when starting emollient was 11 days (IQR 7–17; n=509), and 452 (89%) of 509 had started applying emollient by day 21. Of families in the emollient group with complete questionnaire data on adherence at each timepoint, 466 (88%) of 532 had satisfactory adherence at 3 months, 427 (82%) of 519 at 6 months, and 375 (74%) of 506 at 12 months. 70% (311 of 442) of families with complete questionnaire data were classed as having satisfactory adherence at all timepoints during the first year. Using a highly conservative estimate that assumed 100% of those with no questionnaire data on adherence (ie, did not complete the questionnaires at 3, 6, or 12 months) did not apply the emollient, the proportion of families in the emollient group classed as

having satisfactory adherence was estimated to be 51% (appendix p 32). On the days families used the intervention, most families chose to apply the emollient once a day (422 [79%] of 532 families at 3 months, 382 [74%] of 517 at 6 months, and 362 [72%] of 506 at 12 months). 93 (17%) of 532 families at 3 months, 104 (20%) of 517 families at 6 months, and 94 (19%) of 506 at 12 months chose to apply the emollient twice a day or more. Most participating families, with 479 (90%) of 533 at 3 months, 460 (89%) of 519 at 6 months, and 425 (84%) of 508 at 12 months, applied emollient to the arms, legs, and trunk. Additionally, most reported they usually applied emollient after a bath: 89% (471 of 532) at 3 months, 85% (441 of 516) at 6 months, and 80% (406 of 508) at 12 months. A median of 5 (IQR 2–5) 500 g containers dispensed over the year equated to about 7 g emollient per day over the first year. No emollient was supplied to the control group, but self-directed use of emollients at least three times per week to most of the body (contamination) occurred in 18% (82 of 457) at 3 months, 17% (62 of 372) at 6 months, and 15% (49 of 324) at 12 months, excluding children with a parental reported doctor diagnosis of eczema and who were therefore likely to be using an emollient to treat their eczema (appendix p 31).

Most infants in both groups were bathed or showered at least every other day (6 months, 81% of emollient group and 78% of control group; 12 months, 87% of emollient group and 87% of control group; 24 months, 90% of emollient group and 91% of control group). A third of participating families (32% of emollient group, 31% of control group) used water only (up to 6 months) and half used baby-specific wash products during the first year. Washing practices were balanced across groups (appendix pp 35–36).

Eczema in the past 12 months (UK working party criteria) at age 2 years was present in 139 (23%) of 598 infants in the emollient group and in 150 (25%) of 612 in the control group (adjusted RR 0·95 [95% CI 0·78 to 1·16]; $p=0\cdot61$; adjusted risk difference $-1\cdot2\%$ [$-5\cdot9$ to $3\cdot6$]; table 2). Sensitivity analyses were consistent with the primary analysis, by use of data from GP records for missing primary outcome data, imputed missing data, and CACE

analysis to evaluate adherence (appendix pp 40–42). Subgroup analyses according to number of first-degree relatives with atopic disease or eczema, *FLG* genotype, season of birth, water hardness, and probiotic use found no evidence of an interaction (appendix pp 42, 44–45).

All other measures of eczema diagnosis were consistent with the primary outcome. There were no differences between groups in visible eczema at 2 years, parent report of a clinical diagnosis of eczema at 2 years, or parent completion of UK working party criteria at 1 and 2 years (table 2). Eczema severity assessed either by a masked assessment of clinician-reported signs (EASI)²⁶ or parent-reported symptoms (POEM)²⁷ was also similar between groups (figure 2), as was time to onset of eczema (appendix pp 47–50). Food allergies to milk, egg, or peanut were confirmed in 41 (7%) of 547 infants in the emollient group and 29 (5%) of 568 in the control group (adjusted RR 1·47, 95% CI 0·93–2·33). The largest difference was in the proportion of infants with confirmed food allergy to egg, with an adjusted RR of 1·56 (95% CI 0·92–2·65). Of the confirmed food allergy diagnoses, 30% (21 of 70; 15 in the emollient group and six in the control group) were made with the oral food challenge and 70% (49 of 70; 26 in the emollient group and 23 in the control group) were by use of the algorithm adapted from the EAT trial.²⁵ The results of other measures of food allergy and food sensitisation were similar (appendix pp 59–61). The proportion of infants with allergic rhinitis, wheezing, and allergic sensitisation to cat dander, grass pollen, and dust mite was similar between groups (table 3). There were no differences in quality of life utility measures (CHU-9D and EQ-5D-5L) between the two groups (table 4).

Parent-reported doctor-diagnosed skin infections during the first year occurred in 89 (15%) of 585 infants in the emollient group and in 67 (11%) of 589 in the control group. Impetigo and unspecified bacterial, viral, or fungal skin infections accounted for the majority and a full breakdown of the type of infection can be found in the appendix (p 62). The mean number of skin infections per child was 0·23 (SD 0·68) in the emollient group and 0·15 (0·46) in the control group (adjusted incidence rate ratio of 1·55, 95% CI 1·15–2·09; appendix p 62). Parent-reported infant slippages within an hour of applying emollients were rare and the frequency was similar between groups: 15 (3%) of 584 in the emollient group and 11 (2%) of 584 in the control group (adjusted RR 1·37, 95% CI 0·63–2·97). None of the slippages resulted in serious injury or admission to hospital.

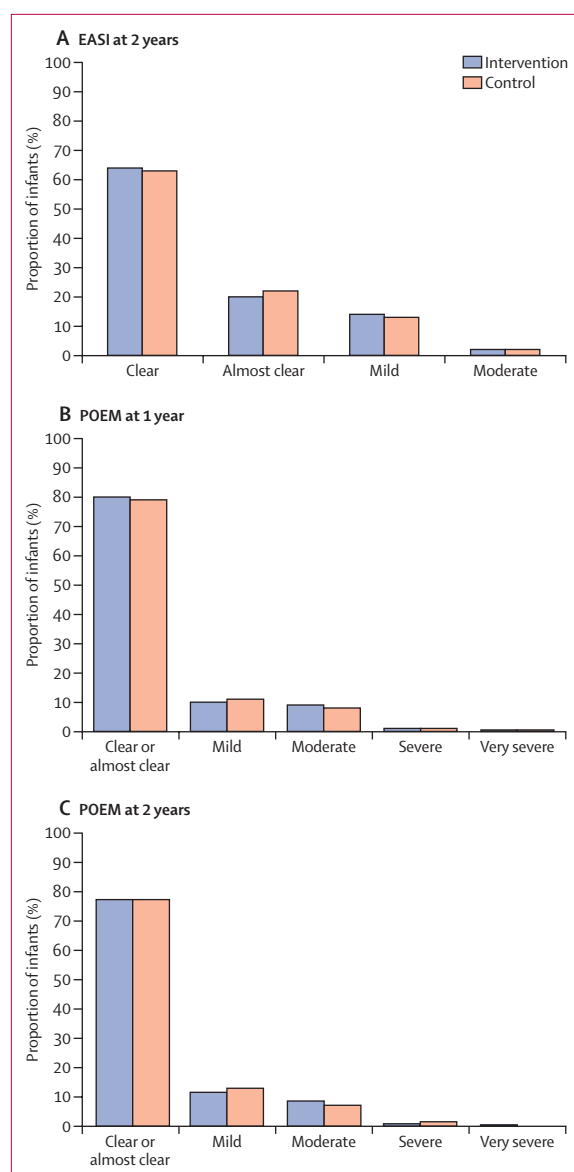


Figure 2: Severity of eczema assessed by clinician-reported signs measured by EASI (masked assessment) and parent-reported symptoms measured by POEM

(A) Severity at 2 years measured by EASI (masked assessment by research nurse) based on categories in Leshem and colleagues.²⁶ Parent-reported severity at 1 year (B) and 2 years (C) measured by POEM, based on categories in Charman and colleagues.²⁷ These analyses include all infants for whom data were available, regardless of their eczema status. EASI=Eczema Area and Severity Index. POEM=Patient-Oriented Eczema Measure.

Discussion

In this multicentre, pragmatic, randomised controlled trial of high-risk infants, we did not find any evidence that regular emollient use for the first year of life can delay, suppress, or prevent eczema at age 2 years. The results for the primary outcome excluded our prespecified relative reduction of 30%. This finding was consistent

	Emollient group	Control group	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Confirmed food allergy				
Confirmed allergy to milk, egg, or peanut at age 2 years*	41/547 (7%)	29/568 (5%)	1.47 (0.93 to 2.33)	2.4% (-0.5 to 5.2)
Confirmed allergy to cow's milk at age 2 years†	9/571 (2%)	8/593 (1%)	1.17 (0.45 to 3.01)	0.2% (-1.2 to 1.6)
Confirmed allergy to egg at age 2 years	33/560 (6%)	22/581 (4%)	1.56 (0.92 to 2.65)	2.1% (-0.4 to 4.6)
Confirmed allergy to peanut at age 2 years	10/555 (2%)	8/572 (1%)	1.29 (0.51 to 3.25)	0.4% (-1.1 to 1.8)
Sensitisation to food allergens‡§				
Allergic sensitisation to milk, egg, or peanut at age 2 years	58/487 (12%)	44/498 (9%)	1.36 (0.94 to 1.95)	2.9% (-0.9 to 6.8)
Allergic sensitisation to milk at age 2 years	14/488 (3%)	11/498 (2%)
Allergic sensitisation to egg at age 2 years	43/490 (9%)	33/499 (7%)
Allergic sensitisation to peanut at age 2 years	18/490 (4%)	16/502 (3%)
Sensitisation to other allergens				
Allergic sensitisation to grass pollen, cat dander, or dust mite at age 2 years¶	50/492 (10%)	48/499 (10%)	1.07 (0.74 to 1.55)	0.9% (-2.8 to 4.5)
Other allergies				
Allergic rhinitis, parent report between age 1 and 2 years	174/572 (30%)	188/598 (31%)	0.97 (0.82 to 1.15)	-0.8% (-6.2 to 4.5)
Wheezing, parent report between age 1 and 2 years	197/572 (34%)	191/598 (32%)	1.07 (0.91 to 1.26)	2.5% (-2.9 to 7.9)

Data are n/N (%) unless otherwise specified. *Food allergy was confirmed by oral food challenge interpreted by a masked allergy nurse using PRACTALL criteria in 21 of 70 participants, or using a validated algorithm adapted from the EAT trial interpreted by a masked expert allergy panel (MJC, NJ, MK, RJB) in 49 of 70.²⁵ †Unadjusted relative risk and difference in risk reported for cow's milk. The model including stratification variables did not converge. ‡≥3 mm skin prick test to fresh milk, raw egg white, or commercial peanut extract. §Adjusted difference in risk and relative risk is not presented for individual allergens (specified in statistical analysis plan that between-group estimates would only be calculated for allergens grouped together). Allergic sensitisation to individual allergens tested is presented in the appendix (p 59). ¶≥3 mm skin prick test to at least one of commercial grass pollen, cat dander, or dust mite extract.

Table 3: Secondary outcomes of confirmed food allergy, sensitisation to common food allergens, allergic rhinitis, and wheezing at age 2 years

regardless of how eczema was defined. There was no evidence that emollients reduced the risk of food allergy; a non-significant increase in food allergy in the emollient group was observed compared with controls. This was largely because of the higher number of participants in the emollient group being diagnosed with egg allergy. Furthermore, we observed an increase in parent-reported skin infections. Notably, we emphasise that our findings relate only to using emollients for preventing eczema, and not the use of emollients for treating eczema.

Strengths of this study include the large sample size and good rates of treatment adherence, high retention for the primary outcome, and low rates of contamination, particularly given that it was a long-term prevention study of healthy infants with little investigator contact. Our study tested an intervention that was acceptable to parents and the use of emollients in the study is likely to closely reflect how emollients are recommended and used in the community.²⁸ Selection, detection, performance, and attrition biases are unlikely to explain the absence of a preventive effect. Eczema was measured using validated criteria, applied by trained researchers masked to the treatment intervention 1 year after use of the emollient had ceased. The primary outcome results were collected by masked researchers, although the diagnostic criteria do include questions that are answered by unmasked parents. Findings were supported by a masked evaluation of eczema that did not rely on parent reporting. Assessing the primary outcome at age 2 years excludes transient eczematous rashes that are common

	Emollient group	Control group	Unadjusted difference in means (95% CI)
CHU-9D at age 2 years*	0.935 (0.070)	0.934 (0.066)	0.001 (-0.007 to 0.009)
EQ-5D-5L parent health-related quality of life at baseline†	0.856 (0.151)	0.852 (0.158)	..
EQ-5D-5L parent health-related quality of life at age 2 years‡	0.921 (0.142)	0.919 (0.130)	0.002 (-0.013 to 0.018)

Data are mean (SD) unless otherwise specified. CHU-9D scores range from 0.33 to 1, with higher scores indicating better quality of life. EQ-5D-5L scores range from -0.594 to 1, with higher scores indicating better quality of life. Of those with data at baseline and age 2 years, 95% were completed by the same responder. The baseline EQ-5D-5L questionnaire was sent to parents in the post shortly after randomisation. CHU-9D=Child Health Utility-9 Dimensions. *n=573 in the emollient group and n=591 in the control group. †n=496 in both the emollient group and the control group. ‡n=573 in the emollient group and n=592 in the control group.

Table 4: Secondary outcome of quality of life

in the first year of life and ensures that any eczema present is not concealed by the application of emollient during the first year—issues that might have accounted for the protective effect of emollients seen in the two previous smaller pilot studies.

The study emollients were chosen because they are commonly used in the UK National Health Service and have a high degree of acceptability to parents, established during preparatory work. Both emollients are a basic formulation containing petrolatum and no ingredients known to have a detrimental effect on the skin barrier, in particular sodium lauryl sulphate. Mechanistic studies showed that these emollients were appropriate to use in such a trial, compared with aqueous cream, which has adverse effects on the skin barrier if used as a leave-on

emollient.^{29,30} We did not use a more complex emollient formulation—for example, one containing ingredients such as ceramides and pH modulators—because when the barrier enhancement for eczema prevention (BEEP) trial was designed, they were not generally available and had a much higher purchase cost. However, a more sophisticated emollient formulation might potentially have a protective effect.

Limitations of the study include a low uptake of the oral food challenges due to several factors. Skin prick tests and oral food challenges were added to the trial once it was underway, so parents were unaware these tests would be offered when they decided to take part. Added to this, many parents were unwilling or unable to travel to the oral food challenge centres, mainly because they had no concern about food allergy in their child or their child had a previously established clinical diagnosis of food allergy. There is also significant uncertainty about the food allergy outcomes, which is not surprising as the study was powered to detect plausible changes in eczema rather than food allergy, which has a much lower incidence. A further limitation was the lower than expected response to interim questionnaires through which adherence was assessed.

The lack of benefit of emollients for prevention of eczema seen in this study was unexpected, particularly when considering the strong signal observed in the previously published pilot trials, and has major implications for the primary prevention of atopic eczema and other diseases.^{13,14} Adherence to the advice to apply emollients once a day might not have been sufficiently high enough to have an effect, or insufficient quantities might have been used during each application. Applying emollients all over the body daily for the first 12 months of life can be difficult to maintain for busy parents of healthy babies. However, data for those who completed questionnaires in which parents were asked about adherence to emollient use since the previous questionnaire showed that adherence was greater than 80% during the first 6 months, which was within our anticipated range, with most parents reporting applying emollient to the whole body. These adherence figures were similar to those seen in our pilot study.¹³ Although adherence decreased to 74% for months 6–12, this was a pragmatic study in which parents had little contact with the research team, reflecting how such a prevention strategy might be delivered in practice. Additionally, this reduction in emollient use was expected because of increased difficulty in regularly applying emollient to infants as they become more mobile as well as general parental fatigue with regards to the routine. There was a small amount of emollient use in the control group in those without any diagnosis of eczema, which could have partially masked any differences between the two groups. Emollients might have to be applied multiple times per day to exert a protective effect, or intervention for longer than a year might be required, but a more demanding

schedule is more difficult to maintain or could be unacceptable to parents. Although the median duration between birth and start of emollient use was only 11 days, even earlier intervention might be required with emollient therapy started closer to birth. The provision of skin care advice to parents in both groups was unlikely to have altered any effect of the emollient, since the advice was based on best practice skin-care advice in the UK and was identical to that used in the pilot trial in which a difference between groups was observed. However, awareness of the importance of using better formulated wash products has increased in recent years.¹³

Although there was no significant difference in occurrence of food allergy between the two groups, any degree of increase in the emollient group was unexpected. The non-significant association between emollient intervention and increased food allergy was seen across several different measures, including objective tests of skin sensitisation. An increase in food allergy is plausible, through enhanced transfer and uptake of food antigens by emollient application, leading to epicutaneous sensitisation.³¹ An ongoing prospective individual patient data meta-analysis³² of at least nine similar studies including the PEBBLES trial (NCT03667651) and the PreventADALL trial³³ will provide more evidence on any association between use of emollients from birth and the risk of developing food allergy. The evidence for increased skin infections with emollients was stronger and could be due to increased inoculation of pathogens on the infant skin during application of emollients,³⁴ disturbance of the skin microbiome, or emollients making the skin more adhesive to bacteria.

Understanding of the properties of the barrier function of the skin in early life has increased and it is possible that other approaches to skin barrier enhancement based on new knowledge might have a preventive effect. These approaches might include using newly developed emollients with enhanced skin barrier properties, or a complex intervention that includes additional stringent measures such as low pH cleansers, infrequent washing, or softened water. Future studies of new candidate emollients or more burdensome skin-care regimens will first need to ensure acceptability to parents and consider the inclusion of behavioural support to ensure adherence for prolonged periods.

Our study does not support the use of emollients for preventing eczema in high-risk infants, a finding supported by PreventADALL, another large trial using a skin barrier enhancing intervention.³³ Our data relate only to prevention of eczema and do not directly challenge the practice of using emollients as first-line treatment for eczema.³⁵

Contributors

HCW conceived the trial and was the chief investigator. HCW, JRC, RJB, RHH, LEB, AAM, KST, SJB, MJR, SL, ELS, MJC, THS, CF, EJM, SD-J, NJ, and MRP all contributed to the conception or design of the trial and the acquisition, analysis, or interpretation of the data. JRC, RHH, EJM, and KST supported the design and conduct of the trial. RS and ST

contributed to the conduct of the trial (data collection and management). RJB led the food allergy assessments aided by NJ, MK, and MRP. AAM and LEB were responsible for the statistical analysis. THS was the health economist. MJC provided expertise in emollients and the skin barrier. SJB was responsible for the genetic analysis. ELS, KST, MJR, SJB, SL, SD-J, and CF all contributed clinical experience of eczema or eczema trials, or both. The manuscript was drafted by HCW, JRC, RJB, RHH, LEB, and AAM; all other authors critically reviewed and revised the manuscript. All authors have approved the final version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

RJB received personal fees from the Dairy Goat Cooperative, Cochrane, DBV Technologies, Prota Therapeutics, ALK Abelo, and from expert witness work, outside of the submitted work. RJB's employing institution Imperial College London has a formal research and innovation partnership with Nestlé, who manufacture and market nutritional products for managing food allergy and sponsor infant nutrition research related to eczema and food allergy. CF received a grant from the EU IMI grant scheme (Horizon 2020), outside of the submitted work. ELS received personal fees from AbbVie, Anacor Pharma, Celgene, Dermira Pharmaceuticals, Eli Lilly and Company, Galderma, and Genentech; and grants from GlaxoSmithKline, LEO Pharma, Menlo Therapeutics, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Valeant Pharmaceutical, Novartis, Dermavant, and Pierre Fabre Dermo Cosmetique outside of the submitted work. ELS also received grants from Anacor Pharma, Eli Lilly and Company, LEO Pharma, Regeneron Pharmaceuticals, MedImmune, Novartis, Roivant Sciences, Vanda Pharmaceuticals, Tioga Pharmaceuticals, Kyowa Hakko Kirin, and Target Pharmaceutical Solutions. MJC received grants and personal fees from Sanofi-Genzyme/Regeneron, Pfizer, Leo Pharma, L'Oreal/LaRoche Possey, Johnson & Johnson, Perrigo/ACO Nordic, and grants from Galapagos, outside of the submitted work. HCW is director of the NIHR Health Technology Assessment Programme and THS is a member of the NIHR Health Technology Assessment Programme commissioning committee. Neither had any part in the decision making for funding this study. All other authors declare no competing interests.

Data sharing

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, will be made available to researchers who provide a methodologically sound proposal to the corresponding author with a signed data access agreement. The study protocol, statistical analysis plan and health economics analysis plan are available on the trial website and the NIHR journals library. All other related documents are available on request to Prof Hywel C Williams as chief investigator of the BEEP trial, at any point.

Acknowledgments

Funding for the trial was obtained from the National Institute for Health Research (NIHR) Health Technology Assessment funding stream (reference 12/67/12). Additional funding for the food allergy and sensitisation tests was obtained from Goldman Sachs GIVES and the Sheffield Children's Hospital Research Fund (reference CA15008). Research nurse support was provided by the NIHR Clinical Research Networks. The trial was developed with and supported by the UK Dermatology Clinical Trials Network (UK DCTN). SJB holds a Wellcome Trust Senior Research Fellowship in Clinical Science (reference 106865/Z/15/Z). CF holds an NIHR Career Development Fellowship (CDF-2014-07-037) and is supported by the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. MK holds an NIHR Transitional Research Fellowship (TRF-2017-10-003). MJR holds a Post-Doctoral Research Fellowship from NIHR (PDF-2014-07-013). The views expressed here are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The UK DCTN is grateful to the British Association of Dermatologists and the University of Nottingham for financial support of the Network. We would like to thank the parents and infants who took time to participate in this trial, and the patients who contributed to trial design by providing helpful feedback at different

stages of trial development. We would like to thank Sheila C Wright (Skin Research Group, Division of Molecular and Clinical Medicine, University of Dundee, UK) for cataloguing and processing the saliva samples for DNA analysis, Daniel Simpkins from the Nottingham CTU for providing the trial database, and Douglas Grindlay (Centre of Evidence Based Dermatology, University of Nottingham, UK) for assistance with literature searches. Chris Partlett (Nottingham CTU) independently validated the analysis for the primary outcome, main food allergy outcome, and skin infection safety outcome. Reuben Ogollah (Nottingham CTU) helped with the complier average causal effect analysis.

References

- 1 Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009; **124**: 1251–58.e23.
- 2 Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1859–922.
- 3 Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: a systematic review and meta-analysis of longitudinal studies. *Allergy* 2018; **73**: 696–704.
- 4 Martin PE, Eckert JK, Koplin JJ, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy* 2015; **45**: 255–64.
- 5 Hill DA, Spergel JM. The atopic march: critical evidence and clinical relevance. *Ann Allergy Asthma Immunol* 2018; **120**: 131–37.
- 6 Drislane C, Irvine AD. The role of filaggrin in atopic dermatitis and allergic disease. *Ann Allergy Asthma Immunol* 2019; published online Oct 14. DOI:10.1016/j.anai.2019.10.008.
- 7 Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med* 2011; **365**: 1315–27.
- 8 Flohr C, England K, Radulovic S, et al. Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *Br J Dermatol* 2010; **163**: 1333–36.
- 9 Brough HA, Liu AH, Sicherer S, et al. Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. *J Allergy Clin Immunol* 2015; **135**: 164–70.
- 10 Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. Overview of reviews the prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. *Evid Based Child Health* 2011; **6**: 1322–39.
- 11 Schmidt RM, Pilmann Laursen R, Bruun S, et al. Probiotics in late infancy reduce the incidence of eczema: a randomized controlled trial. *Pediatr Allergy Immunol* 2019; **30**: 335–40.
- 12 Garcia-Larsen V, Ierodiakonou D, Jarrold K, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *PLoS medicine* 2018; **15**: e1002507.
- 13 Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014; **134**: 818–23.
- 14 Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014; **134**: 824–30.e6.
- 15 Kelleher M, Dunn-Galvin A, Hourihane JO, et al. Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. *J Allergy Clin Immunol* 2015; **135**: 930–05.e1.
- 16 Lowe AJ, Laung DYM, Tang MLK, Allen KJ. The skin as a target for prevention of the atopic march. *Ann Allergy Asthma Immunol* 2018; **120**: 145–51.
- 17 Wren K, Nohlgard C, Nyberg F, et al. Treatment with a barrier-strengthening moisturizing cream delays relapse of atopic dermatitis: a prospective and randomized controlled clinical trial. *J Eur Acad Dermatol Venereol* 2009; **23**: 1267–72.
- 18 Chalmers JR, Haines RH, Mitchell EJ, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. *Trials* 2017; **18**: 343.

For the trial website see <https://www.nottingham.ac.uk/research/groups/cebdl/projects/1eczema/beep-maintrial.aspx>.

For the NIHR journals library see <https://www.journalslibrary.nihr.ac.uk/programmes/hta/126712/#/>

- 19 The National Institute for Health and Care Excellence. Postnatal care up to 8 weeks after birth. 2015. <https://www.nice.org.uk/guidance/cg37> (accessed March 17, 2017).
- 20 Sandilands A, Terron-Kwiatkowski A, Hull PR, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007; **39**: 650–54.
- 21 Paternoster L, Savenije OEM, Heron J, et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. *J Allergy Clin Immunol* 2018; **141**: 964–71.
- 22 Williams HC, Burney PG, Pembroke AC, Hay RJ. The UK Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; **131**: 406–16.
- 23 Simpson EL, Keck LE, Chalmers JR, Williams HC. How should an incident case of atopic dermatitis be defined? A systematic review of primary prevention studies. *J Allergy Clin Immunol* 2012; **130**: 137–44.
- 24 van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. *Cochrane Database Syst Rev* 2017; **2**: CD012119.
- 25 Kelleher M, Jay N, Perkin MR, et al. An algorithm for diagnosing IgE-mediated food allergy in study participants who do not undergo food challenge. *Clin Exp Allergy* 2020; published online Jan 30. DOI:10.1111/cea.13577.
- 26 Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol* 2015; **172**: 1353–57.
- 27 Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating patient-oriented eczema measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol* 2013; **169**: 1326–32.
- 28 Ridd MJ, Roberts A, Grindlay D, Williams HC. Which emollients are effective and acceptable for eczema in children? *BMJ* 2019; **367**: l5882.
- 29 Danby SG, Al-Enezi T, Sultan A, Chittock J, Kennedy K, Cork MJ. The effect of aqueous cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis. *Br J Dermatol* 2011; **165**: 329–34.
- 30 Danby SG, Chalmers J, Brown K, Williams HC, Cork MJ. A functional mechanistic study of the effect of emollients on the structure and function of the skin barrier. *Br J Dermatol* 2016; **175**: 1011–19.
- 31 Brough HA, Simpson A, Makinson K, et al. Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. *J Allergy Clin Immunol* 2014; **134**: 867–75.e1.
- 32 Kelleher M, Cro S, Cornelius V, et al. Skincare interventions in infants for preventing eczema and food allergy. *Cochrane Database Syst Rev* 2020; **2**: CD013534.
- 33 Skjerven HO, Rehbinder EM, Vettukattil R, et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. *Lancet* 2020; published online Feb 19. [https://doi.org/10.1016/S0140-6736\(19\)32983-6](https://doi.org/10.1016/S0140-6736(19)32983-6).
- 34 Glatz M, Jo JH, Kennedy EA, et al. Emollient use alters skin barrier and microbes in infants at risk for developing atopic dermatitis. *PLoS One* 2018; **13**: e0192443.
- 35 The National Institute for Health and Care Excellence. Atopic eczema in under 12s: diagnosis and management. 2007. <https://www.nice.org.uk/guidance/cg57> (accessed Dec 5, 2019).